REMARKS

Upon entry of the amendments herein, claims 1-12, 14 and 15 remain pending in the application. Claims 1 and 4 have been amended herein. No new matter has been introduced by any of these amendments.

Claim 4 has been objected to for lack of clarity. The claim has been amended along the lines suggested by the Examiner.

Claims 1-12, 14 and 15 have been rejected under 35 USC §112, second paragraph as being indefinite. In particular, the Examiner raises issues with respect to the language in parts (b) and (c) of claim 1. This claim has been amended along the lines suggested by the Examiner.

Claims 9 and 15 have been rejected under 35 USC §112, first paragraph as not being enabled by the specification; the Examiner raises an issue with respect to the vectors recited in these claims and the proper deposit thereof. The Examiner asserts that "there is no indication in the specification as to a deposit made or public availability of such deposit." The Examiner is in error in this assessment. On page 20 of the instant specification, under the heading DEPOSIT OF MICROORGANISMS, is clearly disclosed that the vectors in

question were deposited under the Budapest Treaty. This notwithstanding, in the interest of expediting prosecution, provided herewith is a Declaration executed by Applicant's agent. In satisfaction of the requirements of 37 CFR §1.808, the Declarant assures that the plasmids in question will be irrevocably and without restriction or condition released to the public upon the granting of a patent from the instant application.

In light of the date that these plasmid deposits were made under the provisions of the Budapest Treaty, and in light of the filing date of the instant application, it is clear that, in accordance with the requirements of 37 CFR §1.806, the deposits will be available beyond the enforceable life of any patent issuing from the instant application.

Claims 1, 2, 4-8, 10-12 and 14 have been rejected under 35 USC §103(a) as being obvious over US 5,200,183 to Tang, et al. in view of the cited publication of Yamada, et al. While acknowledging that the primary reference does not teach a DNA construct with components from *P. pastoris*, and that it does not teach expression of heterologous proteins in *P. pastoris*, the Examiner asserts that the Yamada reference makes up for the gaps in the Tang reference disclosure.

However, as Applicant has pointed out in the past, the situation is much more complex than the Examiner has recognized. As Applicant has pointed out in the instant application, successful expression of a heterologous protein in active, soluble and secreted form depends on many factors, including correct choice of signal peptide, proper construction of the fusion junction between the signal peptide and the mature protein, growth conditions and other factors.

The Examiner has asserted that Applicant has not provided "any evidence or arguments as to why one of skill in the art would not have been motivated to combine the teachings...." However, Applicants wishes to remind the Examiner that much evidence and various arguments have been provided to this effect. Said arguments and showing are no less valid than the reasons put forth by the Examiner in attempting to justify the rejection. Some of these arguments and showings are provided below, as they should be reiterated and emphasized.

With all of the complexities of making a viable construct leading to a viable expression system, it is not enough merely to have a teaching of various components spread among various references to motivate combination of said teachings to arrive at the instant invention.

Even if the subject matter of the secondary reference could be viewed, in combination with the teachings of the primary reference, as suggesting a general avenue for the exploration of additional constructs for the purpose of expression of other heterologous proteins, such as claimed in the instant application, such a suggestion would still not meet the proper standard for finding obviousness. At the very most, this could only possibly be considered to make it obvious to try to obtain the instant invention, rather than making the present invention obvious to do.

It is well established that the standard of nonobviousness under 35 U.S.C §103 is *not obvious to try, but obvious to do*. (See In re O'Farrell, 853 F.2d 894, 7USPQ2d 1673 (Fed. Cir. 1988).) As determined in O'Farrell, an invention that is obvious to try is nevertheless nonobvious when the prior art makes it obvious to explore a new technology or general approach, for example freeze-drying, that seemed to be a promising field of experimentation, but where the prior art gives only general guidance as to the particular form of the claimed invention or how to achieve it. The courts have also rejected an "obvious to experiment" approach; selective hindsight is no more applicable to the design of experiments than it is to the combination of prior art teachings. (See In re Dow Chem. Co. 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988).)

In the response to the previous final rejection, Applicant provided the Examiner with a copy of the reference of Ratner as one portion of evidence of the unpredictability in the field and how daunting a prospect the devising of the instant invention would be to one of skill in the art. However, the Examiner merely dismissed the Ratner reference as having been published six years before the priority date of the instant application; the Examiner did not comment on the various teachings of Ratner pointed out by Applicant that would lead one of skill in the art away from trying to produce the instant invention.

The Examiner has pointed out the amount of time elapsing between publication of the Ratner reference and filing of the instant application, implying that knowledge obtained in the intervening years contravenes the cited disclosure of Ratner. However, one or two instances of success in that time do not overcome the overwhelming battery of evidence teaching the complexities and uncertainties attendant upon devising an invention such as the instant invention and teaching that each case brings its own problems and considerations. Given all these complexities and uncertainties and given further the complex glycosylation pattern of BSSL, making proper processing of the expressed protein into an active form especially difficult, one can make the case that the amount of time elapsing between Ratner's publication and the filing of the

instant application is indicative of the lack of motivation to make the instant invention in the first place.

In this vein, Applicant wishes to remind the Examiner of the following pertinent points from the Ratner reference:

1) In the first paragraph on page 1129, it is disclosed that optimal expression of a given protein depends on a number of considerations, among them whether the protein is expressed intracellularly or secreted into the medium; the need for appropriate glycosylation, refolding and other posttranslational modifications; and the possibility of antigenicity.

2) In the second paragraph on page 1129, both *S. cerevisiae* and *P. pastoris* are mentioned in connection with attendant uncertainty as to whether products therefrom are appropriately glycosylated.

3) In both the third paragraph on page 1129 and the first paragraph on page 1133 is addressed the idea that each evaluation of a system must be done on a case-by-case basis and that each system is protein specific.

4) In the beginning of the third paragraph on page 1133, it is stated that: "Genzyme's reluctance to consider a license was compounded by questions about the biological activity of the

protein grown with *P. pastoris*--particularly t-PA. 'Their leading example--t-PA--is not biologically active,'...."

It is clear from the Ratner reference that, at the filing date of the instant application, there was significant unpredictability in the art of successful heterologous expression in yeast. The uncertainty and unpredictability is further enhanced when one adds to this the necessity for expression of a large, heavily glycosylated human protein in correctly processed and biologically active form and at high levels.

The prior art teaches that hBSSL is a large, glycosylated protein. hBSSL has many *O*-glycosylation sites which will be glycosylated to varying sizes and complexities due to various factors. The *N*- and *O*-linked carbohydrates in proteins in mammalian cells are quite different from each other and very different from those in yeast, both in carbohydrate content and structure. Further, oligosaccharide structures attached to proteins are also different.

Glycosylation plays an important role in the proper folding of recombinant proteins, as the amino acids are assembled during protein synthesis in the host cells. In the case of hBSSL, a heavily glycosylated protein, one of skill in the art at the time of the present invention would not have been able to

predict, and, in fact, would not have expected, that a *Pichia pastoris* recombinantly-expressed hBSSL protein would be appropriately glycosylated and enzymatically active. It cannot even be concluded, based on the present knowledge in the field, that a given gene would be expressed in a biologically useful way in a heterologous expression system, and the uncertainty was even greater at the time of filing of the instant application.

Another factor contributing to the inability of a person skilled in the art, even at the present time, to predict or appreciate that a given protein, in this case hBSSL, will be expressed in a biologically active form stems from the known fact that some recombinantly expressed proteins are subject to endogenous proteolytic degradation. It is for this reason that protease-deficient mutant host strains are generally used for recombinant expression of heterologous proteins. Such "sick" strains may not be suitable, however, for expression of large protein genes such as the 3-kB gene required to encode the 722-amino-acid hBSSL protein. Until the present invention, then, there could have been no certainty for those in the field that hBSSL expressed in *P. pastoris* cells would not be subjected to endogenous cellular proteolytic degradation. This is yet another factor that would have worked against motivation to make or even try to make the instant invention.

The Examiner has characterized the vectors integral to the instant invention as novel. In view of the above arguments and the state of the art at the time of the instant invention, there was not sufficient motivation to make the instant invention and, hence, the invention is also nonobvious.

For the same reasons set forth above, the rejection of claim 3 under 35 USC §103(a) as being obvious over the Tang patent in view of the Yamada reference and further in view of the Martinez application; the rejection of claims 1, 2, 4-8, 10-12 and 14 on the grounds of obviousness-type double patenting over US 5,827,683 in view of Yamada; and the rejection of claim 3 on the grounds of obviousness-type double patenting over US 5,827,683 in view of Yamada and further in view of Martinez cannot stand and should be withdrawn.

The Examiner has requested that a clean copy of the pending claims be submitted. However, in view of the recent PTO guidelines for submission of amendments, a single marked-up list of the claims has been provided. This list, with status identifiers, contains all of the presently pending claims, whether amended herein or not.

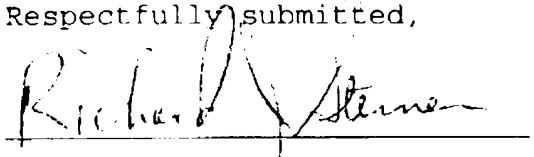
Applicant has amended the claims in accordance with the Examiner's suggestions to address the objections and rejections under §112 of the statute. Furthermore, the claimed subject

matter is patentably distinct over the recited prior art in view of the lack of motivation provided thereby and, hence, the Examiner's failure to make a *prima facie* case of obviousness. Reconsideration and allowance of pending claims 1-12, 14 and 15 are respectfully requested.

The Commissioner is hereby authorized to charge any fees which may be due in connection with this communication to Deposit Account No. 23-1703.

Dated: August 21, 2003

Respectfully submitted,



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